EVALUATION OF CHLOROPICRIN

AS A TOXIC AIR CONTAMINANT

Executive Summary

Department of Pesticide Regulation
California Environmental Protection Agency

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Introduction

The Department of Pesticide Regulation (DPR) conducts risk assessments for pesticides used in California to determine whether the use poses a present or potential human health hazard in California. Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations. This type of assessment includes a quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. After the completion of the risk assessment, the risk management phase takes place at DPR. Risk management refers to the process by which regulatory actions are chosen to deal with hazards identified in the risk assessment process. Risk managers consider scientific evidence and risk estimates, along with statutory, engineering, economic, social, and political factors, in evaluating alternative regulatory options and choosing among those options.

Risk assessments are mandated by the California Food and Agriculture Code (CFAC) Section 12824. Under CFAC 12824, risk assessments are prepared to evaluate the potential exposures of various population groups, which may include workers, residents, and bystanders, depending on how the pesticide is used. A bystander is defined as any person not directly involved with the pesticide application process who is in the vicinity of the application site. The Toxic Air Contaminant Act of 1983 (sometimes referred to as Assembly Bill 1807) established a procedure for identification and control of toxic air contaminants (TACs) in California. The statute defines TACs as air pollutants that may cause or contribute to an increase in mortality or in serious illness, or that may pose a present or potential hazard to human health. DPR's TAC program focuses on the evaluation and control of pesticides in ambient community air.

This report summarizes the risk assessment under AB 1807 mandates for public exposures to chloropicrin in any of 54 products currently registered in California. In preparing this report, DPR staff reviewed pertinent scientific literature and reports. Based on the results of this evaluation, the Director of DPR will determine whether chloropicrin is a TAC, and whether mitigation measures are needed to reduce chloropicrin exposure of the general population in California. If chloropicrin is designated a TAC, the risk management provisions of the law mandate that DPR determine the need for and develop appropriate control measures for chloropicrin uses in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), the Air Resources Board (ARB), the air pollution districts, air quality management districts, and county agricultural commissioners of the affected counties.

What is contained in the report?

This report evaluates the potential for public exposure to chloropicrin and includes the following:

A review of the available scientific evidence on chloropicrin regarding physical properties, sources in the environment, and fates in the environment; a summary of toxicology studies conducted with chloropicrin; estimates of public exposure to airborne chloropicrin; and an assessment of the risk to the public resulting from current or anticipated exposure to airborne chloropicrin.

What is chloropicrin, what are the primary sources of chloropicrin in the environment, and how it is used?

Chloropicrin is a fumigant pesticide; fumigants are gases that during use fill an area, such as a building or soil in a field, and poison targeted pests. Chloropicrin has a low odor threshold and causes sensory irritation at very low concentrations, and in addition to its use as a pesticidal active ingredient it also is

added as a warning agent to the odorless fumigant methyl bromide; small amounts of chloropicrin are also co-applied in structural fumigations with sulfuryl fluoride, as a warning agent. There are 54 registered products containing chloropicrin in California, including seven products intended solely for manufacturing or reformulation use and eight products where chloropicrin is used as a warning agent. Chloropicrin-containing products are available in both pressurized and non-pressurized containers, as compressed liquids in cylinders or liquid solutions containing emulsifiers. Many are mixtures with methyl bromide or 1,3-dichloropropene.

Chloropicrin's chemical formula is CCl_3NO_2 and its molecular weight is 164.38 grams/mole. Pure chloropicrin is a colorless liquid, with a boiling point of 112 °C. Chloropicrin is highly soluble in water with solubility of 2,000 milligrams per liter at 25 °C. It is volatile, with a vapor pressure of 23.2 millimeters of mercury (mm Hg) at 25 °C; the corresponding Henry's Law Constant is 0.00251 atmosphere-cubic meter per mole. The octanol-water partition coefficient (K_{ow}) of chloropicrin is estimated to be 269.

The primary source of chloropicrin in the environment is pesticide applications in which chloropicrin is either a fumigant active ingredient or a warning agent. Additionally, chloropicrin occurs in small amounts as a minor, transient byproduct of reactions between organic matter and certain water treatment chemicals used in chlorination and other oxidative water disinfection treatments.

Chloropicrin use in California increased from 2,494,606 pounds (1,133,912 kilograms or kg) in 1993 to 5,494,541 pounds (2,497,519 kg) in 2007. The total number of acres treated with chloropicrin has not increased, however, ranging from 42,702 acres (17,281 hectares or ha) in 1993 to 61,323 acres (24,817 ha) in 1999, and averaging 53,974 acres (21,843 ha) during the 15-year interval of 1993 – 2007. At least 99% of chloropicrin use each year is in pre-plant soil fumigation; use on strawberry fields accounts for an average of 68% of pounds of chloropicrin applied and 53% of acres treated. The top five counties in which chloropicrin was used in the 5-year interval 2003 – 2007 are Monterey, Ventura, Santa Barbara, Santa Cruz, and Siskiyou; together, they accounted for 76% of statewide use.

What is the fate of chloropicrin in the environment?

Following application to soil, chloropicrin rapidly diffuses through the soil in all directions, then dissipates quickly, with half-lives ranging from approximately an hour to several days. Volatilization is the major pathway through which chloropicrin dissipates from soil, but chloropicrin is also degraded through biotic and abiotic reactions. In water, chloropicrin can persist for several days in the absence of light, but it degrades rapidly when subjected to light of suitable wavelengths, with half-lives ranging from 6 hours to 3 days. Under reducing conditions, chloropicrin also reacts quickly, undergoing reductive dechlorinations. In air, chloropicrin is reactive, undergoing rapid photodegradation to phosgene and nitrosyl chloride, with an estimated half-life of 18 hours under constant illumination in the laboratory.

Who will be exposed to chloropicrin, and what are the exposure levels?

Individuals might be exposed to chloropicrin if they live, work, or perform other activities adjacent to structures or fields that are being treated or have recently been treated (bystander exposure). Members of the public can potentially be exposed to chloropicrin in indoor air if they enter a structure following fumigation. Also, air monitoring studies in Kern, Monterey, and Santa Cruz counties suggest that chloropicrin exposures to the public are possible from airborne residues that have moved away from a pesticide application. Exposures to chloropicrin in ambient air away from applications are anticipated to be equal to or less than bystander exposures to chloropicrin, as the highest pesticide concentrations

in air occur adjacent to an application. Bystander exposure estimates are thus health-protective estimates for such ambient air exposures, and are considered to also represent all ambient air exposures to chloropicrin.

Screening estimates are provided in this report, expressed as concentrations. Although members of the public might potentially be exposed to a range of chloropicrin concentrations, for screening risk assessment purposes the highest realistic exposures to bystanders, based on available data, are reported; if screening estimates result in acceptable risk, then lower exposures will, as well. Screening estimates are calculated using the maximum application rate allowed in California, along with any other conditions that would tend to increase exposure. Ideally, screening estimates provide the maximum realistic exposure. To achieve their purpose it is critical that screening estimates do not underestimate exposure. In this report, exposures are expressed as concentrations. Exposure durations are short-term (i.e., intervals of 7 days or less), seasonal (intermediate-term intervals, lasting from one week to one year) and annual. For bystanders, the exposures are primarily short-term, although seasonal and annual exposures are possible for individuals living and working in areas where applications frequently occur.

Exposure estimates for individuals next to fields during or following chloropicrin applications were calculated from concentrations based on air dispersion modeling of direct flux measurements during application site monitoring. Short-term exposure estimates for bystanders were as follows: 110,000 micrograms per cubic meter ($\mu g/m^3$, equivalent to 16,000 parts per billion or ppb) for 1-hour exposures, 44,000 $\mu g/m^3$ (6,500 ppb) for 8-hour exposures, and 7,400 $\mu g/m^3$ (1,100 ppb) for 24-hour exposures. Seasonal bystander exposure was estimated at 490 $\mu g/m^3$ (73 ppb), annual exposure was estimated at 160 $\mu g/m^3$ (24 ppb), and the lifetime exposure estimate was 70 $\mu g/m^3$ (10 ppb).

Exposures of bystanders adjacent to a structural fumigation with chloropicrin as a warning agent were estimated at 73 $\mu g/m^3$ (11 ppb) for a 1-hour duration, 16 $\mu g/m^3$ (2.4 ppb) for an 8-hour exposure, and 6.2 $\mu g/m^3$ (0.92 ppb) for a 24-hour exposure. Exposures of bystanders adjacent to an enclosed space fumigation with chloropicrin were estimated at 2,400 $\mu g/m^3$ (360 ppb) for a 1-hour duration, 680 $\mu g/m^3$ (100 ppb) for an 8-hour exposure, and 210 $\mu g/m^3$ (31 ppb) for a 24-hour exposure; annual and lifetime exposure estimates were both 1.2 $\mu g/m^3$ (0.18 ppb). These concentrations were based on monitoring conducted during a structural fumigation with chloropicrin as a warning agent. Indoor air monitoring following fumigation and aeration in the same study was used to estimate exposure of 140 $\mu g/m^3$ (21 ppb) for a 24-hour duration for individuals returning to fumigated structures. No seasonal, annual, or lifetime bystander or indoor air exposures from structural fumigation activities are anticipated.

What are the potential health effects from acute and repeated exposures to chloropicrin?

The primary effects observed with short and long-term exposure to chloropicrin are sensory and respiratory irritation. The mechanism of action for chloropicrin is not well understood, but may involve reaction with thiol groups of certain proteins, such as glutathione and hemoglobin. A sensory irritation study was conducted using human subjects with exposures up to one hour. Eye irritation was the most sensitive endpoint. A No-Observed-Effect Level (NOEL) was not observed with the 1-hr exposure. Using a benchmark dose (BMD) analysis, the 1-hr NOEL was estimated to be 26 ppb. Animal studies were used to evaluate longer-term exposures. The lowest acute NOEL in an animal study was seen in an inhalation developmental toxicity study in rabbits based on mortalities, nasal discharge, reduced body weights and food consumption and red discoloration in lungs in the pregnant females. After adjusting for differences in breathing rates between rabbits and humans (children), the 8-hr and 24-hr NOELs were estimated to be 270 and 92 ppb. A BMD analysis was performed on the

mouse and rat 90-day inhalation studies to determine what was the most sensitive endpoint. After adjusting for breathing rate differences between rats and humans (children), the subchronic NOEL was estimated to be 35 ppb (children) based on rhinitis in females rats. A BMD analysis was also performed to determine the most sensitive endpoint in the rat and mouse chronic inhalation studies. After adjusting for species difference in breathing rate, the most sensitive endpoint with chronic inhalation exposure to chloropicrin was bronchiectasis in female mice with a NOEL of 32 ppb (children).

Several developmental and reproductive effects were seen in studies including reduced number of implantation sites, increased pre- and post-implantation losses, late-term abortions, and visceral and skeletal variations in fetuses. The NOELs for fetal or pup effects were equal to or higher than the maternal or parental NOELs, suggesting there is no increased pre- or post-natal sensitivity to chloropicrin. Direct exposure to the neonates, however, was not evaluated.

Is there any potential cancer risk from exposure to chloropicrin?

The genotoxicity data for chloropicrin were mixed. Due to positive results in numerous genetic toxicity assays, especially the gene mutation assays, DPR concluded that a genotoxic mode of action for tumor formation may be possible. In the chronic inhalation study in mice, there was a slight increase in pulmonary adenomas and carcinomas in female mice, that was statistically significant by trend analysis and pair-wise comparison when survival was taken into consideration. In one chronic oral study in rats, a slight, but statistically significant increase in fibroadenomas was seen in females, although the incidence was within the historical control range for this laboratory. DPR concluded the increase in lung tumors with inhalation exposure and in mammary tumors with oral exposure was sufficient to warrant a quantitative assessment of carcinogenicity. The cancer potency of chloropicrin was estimated to range from 1.3 $(mg/kg/day)^{-1}$ (maximum likelihood estimate - MLE) to 2.2 $(mg/kg/day)^{-1}$ (95^{th} percent upper bound - 95%UB) based on the incidence of lung tumors in female mice.

Does the concentration of chloropicrin in the ambient air pose a potential health hazard for humans?

The risk for non-carcinogenic health effects can be expressed as a margin of exposure (MOE) which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable when the NOEL is based on an animal study, assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower distribution of the overall human population and the sensitive subgroup. When the NOEL is based on a human study, a MOE of 10 or greater is considered adequate allowing for intraspecies variation in sensitivity. Since sensory irritation involves a direct-acting mechanism of toxicity where toxicokinetic variation among individuals is not anticipated, a MOE of 3 may be adequate. California regulations state that if the air concentrations of a pesticide are not 10-fold below the reference concentration that is considered protective of human health, it meets the criteria to be listed as a toxic air contaminant. This is equivalent to the MOEs being greater than 30 when the NOEL for sensory irritation in humans is used or 1,000 when an animal NOEL is used. For cancer, the negligible risk level is generally considered a risk of less than one extra case in a million people. If the cancer risk is greater than one in 10 million people, it meets the criteria for listing it as a toxic air contaminant.

The potential health risks from bystander exposure to chloropicrin following soil fumigation are of concern since all of the MOEs were less than target MOE of 100 for both children and adults. The bystander acute MOEs for soil fumigation are clearly of concern since they are all less than 1 and

strongly suggest mitigation is needed. In particular, the 1-hr exposures are of great concern since the MOEs are orders of magnitude lower than the target MOE of 3 based on the NOEL for sensory irritation in the human study. The bystander seasonal and chronic MOEs for soil fumigation were greater than 1 (except for bedded tarped application), but still less than 100, which is the target MOE. The carcinogenic risk for bystanders following soil fumigation is also of concern since the risk estimates were orders of magnitude greater than the negligible risk level. The air concentrations of chloropicrin following structural fumigation are lower than following soil fumigation, but the bystander 1-hr exposures are still of concern (i.e., MOEs are slightly less than 3). Although the bystander 8-hr and 24-hr MOEs are greater than 100, they are less than 1,000. The indoor air concentrations of chloropicrin following structural fumigation are also of concern since the 24-hr MOEs were less than 100. The acute MOEs for bystanders following enclosed space fumigation with chloropicrin are of concern since they are all significantly less than their target MOEs. The annual MOEs for bystanders of enclosed space fumigation are not of concern. However, the carcinogenic risk estimates for enclosed space fumigation are significantly greater than the negligible risk level and, therefore, of concern. Chloropicrin clearly meets the criteria for listing it as a toxic air contaminant based on the off-site air concentrations following soil fumigation, structural fumigation and enclosed space fumigation.

Does any degradation product of chloropicrin pose a potential health hazard?

At this time, there is only limited evidence that a degradation product or metabolite of chloropicrin may be more toxic than the parent compound. The dichloro- and monochloro- metabolites of chloropicrin have been shown to be less potent inhibitors than the parent compound of the enzymes, pyruvate dehydrogenase and succinate dehydrogenase, presumably due to reaction with the thiol groups in their active sites. These enzymes may be targets for the lacrimatory effect of chloropicrin. No inhibition of these enzymes was observed with the nitromethane metabolite. On the other hand, the dehalogenated metabolites appear to be as mutagenic or more mutagenic than chloropicrin, suggesting that the mutagenicity of chloropicrin may be due to its dechlorinated metabolites or reactive intermediate GSH conjugates of the metabolites.